Gly for Asp[96]; Thr for Ala[103] or Ile[106]; Ser for Leu[118]; Gly for Asp[124]; Thr for Lys[138]; Pro for Ser[146]; Asp for Val[164]; Leu for Gln[177]; Asp for Gly[179]; Gly for Glu[192]; deletion for Cys[193]; His for Leu[197]; Ser for Ile[221]; Leu for Asn[233]; Leu for Ser[273]; deletion for Thr[278]; Ala for Asp[285]; Glu for Lys[286]; Ser for Gly[310]; Arg for Met[370]; Ile for Ser[379]; Ser for Phe[394]; Ala for Glu[417]; Gly for Glu[459]; Ser for Ile[476]; Thr for Ile[482]; Thr for Ile[551]; His for Tyr[586]; Lys for Ile[648]; Ala for Ser[686]; His for Cys[687]; Thr for Ile[759]; Ile for Asn[776]; Asp for Gly[781]; Gly for Glu[782]; Gly for Ser[827]; Ala for Asp[832]; Arg for Pro[892]; Thr for Glu[893]; Asp for Thr[894]; or Leu for Glu[896], wherein the numbering of the amino acids corresponds to the numbering adopted for SEQ ID NO:56.--

B7 Cont

REMARKS

The foregoing amendments and the following remarks are submitted in response to the Office Action mailed January 7, 1998.

Applicants have amended the Specification at page 19, line 8 to correct a spelling error, replacing the correctly spelled "interspecies". It would be clear to one skilled in the art that this is what was intended, in that the mouse and human species are compared as examples of activity interspecies.

Applicants have also amended the Specification at page 19, line 18 to correctly refer to the appropriate SEQ ID NOS: (SEQ ID 1, 3, 5, 7 and 9) which, collectively, contain the amino acid sequences of the OB-R variants depicted in Figure 2B and further described on page 20 and pages 25-26 of the Specification.

Applicants have further amended the Specification at page 19, line 24 to correctly refer to the appropriate SEQ ID NOS: (SEQ ID 2, 4, 6, 8 and 10) which, collectively, contain the nucleic acid sequences of the OB-R variants depicted in Figure 2B and further described on page 20 and pages 25-26 of the Specification.

Applicants have amended the Specification at page 25, line 15 to clarify the reference to the published OB-R, specifically that disclosed in Tartaglia et al. [Cell 83: 1263-1271], and to further incorporate correct reference to the SEQ ID NOS: which now provide the complete amino acid sequences of the published mouse and human OB-R of Tartaglia et al. Applicants submit herewith a revised SEQ ID listing, now including these referenced SEQ ID NOS,

specifically SEQ ID NOS: 55-56. Applicants submit that this does not constitute new matter, particularly in view of the Specification's reference to Tartaglia at page 4, lines 25-27, and further in the incorporation of Tartaglia et al. by reference in its entirety at page 93, lines 2-3.

The foregoing amendments to page 26, line 21 were made to further clarify the Specification in the characterization of the specific variant OB-Re. More specifically, at page 26, line 20-21, the Specification states that OB-Re "corresponds to published OB-R to His ^{796}, where it diverges." Applicants have now amended this description of the OB-Re variant to clarify that it corresponds to the published OB receptor sequence up to and including His ^{796}, "with a different nine amino acid sequence C-terminal to His ^{796} ". Figure 2B of the Specification is a schematic drawing of several splice variants of the leptin receptor (OB-R). Similar to the variant OB-Rd, which corresponds to published OB-R with a different eleven amino acid sequence C-terminal to Lys^{889} , it is clear from Figure 2B to one skilled in the art that variant OB-Re contains new/different amino acids than the published OB receptor after (i.e., C-terminal to) His ^{796}, namely the nine amino acids GMCTVLFMD. Applicants submit that this does not introduce new matter into the Specification, because it is clear from Figure 2B and from the Specification that, similar to variant OB-Rd, variant OB-Re contains these different amino acids versus the published OB receptor sequence C-terminal to His ^{796} .

Status of the Claims

Claims 20-28, 34-48 and 51-52 are pending in the Application. Claims 20 and 23 have been canceled. Claims 21, 22, 24, 27 and 34 have been amended and new Claims 67-68 are presented in order to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amended claims can be found generally through Applicants' Specification.

Particularity and Distinctiveness of the Claims

The Examiner has rejected Claims 20-28, 34-48 and 51-52 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter Applicant regards as the invention.

The Examiner has rejected claims 20-23 and their dependent claims (claims 34-35, 37, 39, 41, 43, 45, 47 and 51) as indefinite for depending on non-elected claims and requests that these claims be put in independent form. By amendment above, Applicants have now canceled claims 20 and 23 and have amended claims 21 and 22 to place them in independent form and Applicants submit that this rejection is now made moot.

The Examiner has rejected claim 21 and its dependent claims as they depend from claim 6 and are indefinite for failing to clearly define the C-terminal. Applicants respectfully disagree. It would be clear to one skilled in the art what is meant by "C-terminal". The claimed nucleic acids encoding OB receptors (previously those of Claim 6, now claimed independently) have a first part (the N-terminal part) followed by a second part (the C-terminal part). Specifically, the now presented claims relate the specific sequence characteristics of the claimed variant OB-R's by describing the sequence present at the N-terminal, or the first part of the sequence, which is followed by specific sequences present at the C-terminal, i.e.: the second part after the N-terminal sequences. The use of this well recognized and descriptive language, combined with the teaching in the Specification, including the schematic drawing of Figure 2B, makes clear to one skilled in the art what is claimed.

The Examiner has rejected claims 21-22 and their dependent claims as they depend from claim 7a, 7b, 9b and 9c as indefinite, incomplete and confusing for failing to recite a point of reference for the sequence and residue numbers referred to therein. By Amendment and as discussed above, Applicant have now amended the Specification to more clearly refer to the published unaltered OB-R sequence for the mouse OB-R (leptin) receptor and for the human (OB-R) leptin receptor as that described in Tartaglia et al. [Cell. 83: 1263-1271 (1995)]. In addition, as discussed above Applicants now present a new and revised SEQ ID listing, which specifically includes the published and unaltered mouse OB-R and human OB-R as SEQ ID NO: 55 and 56 respectively. Applicants have now amended Claims 21 and 22 as independent claims and further more clearly refer to the specific SEQ ID NOS: which are the relevant published and unaltered mouse or human OB-R sequences.

The Examiner has rejected claims 21-22 and their dependent claims as they depend from claims 5-6, 9 and any claim that refers to the OB receptor by the designations of OB-Ra, OB-Rb,

OB-Rc, Ob-Rd and OB-Re, which the Examiner asserts are indefinite, confusing and contradictory for failing to be consistent in their meaning. Applicants respectfully submit that what is meant by the designations OB-Ra, OB-Rb, OB-Rc, OB-Rd and OB-Re is clear to one skilled in the art, particularly in view of the teachings in the Specification, including the specific description and characterization of each of these variant leptin receptors, for instance in Figure 2B. In addition, the complete amino acid sequence of variant receptors OB-Ra, OB-Rb, OB-Rc, OB-Rd and OB-Re are provided in the Specification as SEQID NOS: 2, 4, 6, 8 and 10, respectively.

The Examiner has rejected claim 24 and its dependent claims as confusing with regard to what is intended by "identifiable". Applicants have now amended claim 24 to recite "amplifiable" in order to clarify what is intended. The Examiner further rejects claim 24 and its dependent claims as confusing with regard to what is intended by "corresponding to" and whether it is the same or a similar DNA sequence. Taking into consideration that slight differences in amino acid sequence can occur, Applicant's claim 27 intends to encompass both precisely corresponding to (i.e., the same DNA sequence) and reasonably corresponding to (i.e., a similar DNA sequence), such that one skilled in the art would readily recognize that these sequences were closely related.

The Examiner has objected to claims 51 and 52 as being duplicates of claims 35-36 despite slight differences in the wording in recitation to a "transgenic" vector. The Examiner asserts that there are no features that distinguish claims 51 and 52 from 35 and 36. Applicants respectfully disagree and submit that one skilled in the art would recognize the difference and distinguishing features. Claims 35 and 36 are directed to any type of vector including vectors suitable for bacterial hosts, etc. The transgenic vector of claims 51 and 52 would be recognized by the skilled artisan as one which is suitable for transgenic expression, for instance in transgenic mice or sheep. The skilled artisan would further recognize the appropriate characteristics necessary or appropriate in any such transgenic vector.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's rejection is obviated and should be withdrawn.

The Specification Enables the Claimed Invention

The Examiner has rejected Claims 20-28, 34-48 and 51-52 under 35 U.S.C. 112, first paragraph, because the Examiner asserts that the Specification "while being enabling for certain variant forms of the OB-R", does not reasonably provide enablement for all the various OB receptors being claimed, specifically for "a) NA encoding an OB-R devoid of characterization as in Claims 20-23 as they depend from claims 1, 5, 8, 9a and 9b; b) for NA that encode for an OB-R with limited characterization, or merely defined by abbreviations as in Claims 21 as it depends from claim 5; c) for any OB-R merely defined by the primers of Claims 24-28; and d) for NA encoding any and all variant OB-R as in Claims 21-23 as they depend from 5, 6g, 7 and 9". Each of the issues a) through d) pointed out by the Examiner with respect to this rejection will be addressed by Applicants below.

The Examiner argues regarding issue a) that the Specification does not reasonably provide enablement for a) NA encoding an OB-R devoid of characterization as in Claims 20-23 as they depend from claims 1, 5, 8, 9a and 9b. By Amendment above Applicants have now canceled relevant Claim 20 and 23 and amended relevant Claims 21 and 22. The Claims now presented refer specifically to characterized OB receptors and do not refer to any OB-R devoid of characterization. The claims in each instance detail specific sequence characteristics, as described in the Specification. Regarding the OB-R of Claim 22, this OB-R is characterized as being a soluble receptor, the nature of which is more specifically described in the Specification, including at pages 17, line 26 through page 18, line 1. In these referenced lines the Specification details the three important structural domains of the OB receptor and describes a specific embodiment, "a receptor of the invention comprises only an extra cellular domain, i.e., it is a soluble receptor". Thus, as described in the Specification and further well recognized by one skilled in the art, a soluble receptor is a receptor which only comprises an extracellular domain, thereby lacking the transmembrane domain and any intracellular domain. As such, the receptor is capable of binding its ligand (in this case, leptin) but is soluble and is not attached to (or through) the cell membrane. Applicants submit that in view of the above discussion and amendments to the claims the Examiners' rejection should be withdrawn.

In issue b), the Examiner asserts that the Specification does not reasonably provide

enablement for NA that encode for an OB-R with limited characterization, or merely defined by abbreviations as in Claims 21 as it depends from claim 5. With regard to enablement of Ob-R defined by abbreviations, as in Claim 21 (as previously dependent from Claim 5, now amended in independent form), Applicants respectfully disagree and assert that the Specification provides a clear and complete characterization of the specific abbreviated Ob-R forms (namely, OB-Ra, OB-Rb, OB-Rc, OB-Rd and OB-Re). Such characterization includes description in the Specification at page 25-26, the schematic drawing of these specifically claimed variants in Figure 2B, and the complete nucleic acid and amino acid sequences of these variant forms which is found in SEQ ID NOS: 1-10.

The Examiner further argues that the Specification does not provide enablement "c) for any OB-R merely defined by the primers of Claims 24-28". Applicants respectfully disagree. The use of the referenced primer sequences of Claims 24-26 to identify DNA molecules which encode on expression a leptin receptor polypeptide, by hybridization and/or PCR, employs standard methods and techniques of the skilled artisan. The Specification further provides guidance and specific teaching of the use of the referenced primer sequences in identifying nucleic acids encoding leptin receptor (OB-R) polypeptides in Example 3 on pages 90-92. In addition, Applicants have now amended Claim 24 to recite a DNA molecule which is "amplifiable" with a PCR probe from the group, in order to more clearly refer to molecules which can be identified through a PCR reaction using any such forward and reverse primers. Thus, in view of the examples and guidance in the Specification and the considerable skill of the artisan, combined with the standard nature of the claimed use of such primer sequences, even as now amended, one skilled in the art could use such primer sequences to amplify any of the DNA molecules claimed without experimentation. With regard to the Examiner's rejection of Claims 27 and 28 "for any OB-R merely defined by the primers" of those claims, Applicants respectfully submit that this rejection is in error in view of the absence of any referenced primers in either of clams 27 or 28.

In issue d), the Examiner asserts that the Specification does not reasonably provide enablement for NA encoding any and all variant OB-R as in Claims 21-23 as they depend from 5, 6g, 7 and 9. Applicants respectfully disagree. In fact, the Specification provides examples,

evidence and guidance for polypeptides representing numerous specific variants of OB-R. The Specification details the cloning and characterization of variant OB receptor polypeptides, specifically OB-Ra, OB-Rb, OB-Rc, OB-Rd and OB-Re. Sequence comparison between the amino acid and nucleic acid sequences of human and mouse OB receptors described herein and in the prior art identifies a number of divergent residues. The skilled artisan is further provided guidance for isolation and characterization of such variants by the examples and evidence in the Specification. Applicants submit that isolating, making and/or testing any such allelic variants involves standard methodology well known to those of skill in the art, particularly in view of the disclosure of the isolation and characterization of five distinct variants in the Specification.

Applicants further submit that it is unnecessary to provide working examples of all embodiments and variants of OB-R so long as there is a sufficient and enabling disclosure to guide the skilled artisan. Applicants submit that, at the date of priority of the instant Application (1-16-96), the isolation, making and testing of variant polypeptides was well known to molecular biologists and part of the repertoire of methods available to one skilled in the art. As of 1996, technology had already been developed and well established which enabled workers of ordinary skill in the art, using the guidance provided by the Specification, to routinely and without undue experimentation prepare any variant OB-R polypeptides encompassed by the present claims. While some experimentation to make and test such polypeptides would be necessary, such experimentation would utilize well known formulae and standard skills and would not constitute undue experimentation.

In view of the foregoing remarks, Applicants submit that the Examiner's rejection under 35 U.S.C. 112, first paragraph may properly be withdrawn.

The 102 and 103 Rejections

The Examiner has rejected Claims 20-28, 34-48 and 51-52 under 35 U.S.C. 102(a) or (e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tartaglia et al or Snodgrass et al. The Examiner states that "In view of the broad manner in which the claims are written, each of the prior art anticipate most of the claims or anticipate portions of

the alternative limitations of the claims". Applicants respectfully disagree and further submit that this rejection is overcome in view of the amended claims now presented and remarks discussed below.

Tartaglia et al disclose the cloning of a human and mouse OB-R, with the nucleic acid and amino acid sequences compared in Figure 8. The OB receptors disclosed by Tartaglia do not teach or disclose the OB variant receptors now claimed by Applicants. The OB-R variants claimed by Applicants are distinct from the human and mouse OB-R disclosed by Tartaglia et al. In the Specification at page 25, line 15 to page 26, line 25, it is noted that "the term OB-R specifically encompasses different splice forms of the polypeptide, including but not limited to the following: "and reference is made to a tabulation of specific example variant splice forms OB-Ra, OB-Rb, OB-Rc, OB-Rd and OB-Re. The characteristics detailed for each of these example variant OB-R's specifically distinguishes them from published OB-R sequence, namely Tartaglia et al. The Specification refers to Tartaglia et al. at page 4, line 25-27:

> However, a recent report of identification of a leptin receptor did not identify any mutations in the ob allele [Tartaglia et al., Cell, 83: 1263-1271(1995)].

As noted in the Specification (including as quoted above), Tartaglia provides no specific teaching, disclosure or description with respect to any such OB variant receptors. With respect to Tartaglia and variant forms, the Examiner comments that "while not [sic] other variant forms were expressly disclose, at several places throughout the citation, there is reference to the possible existence of other splice variants". The Examiner further asserts that this mere reference to the "possible existence of other splice variants" renders obvious the instant claims that recite a DNA sequence that is different from that disclosed in the prior art. Applicants respectfully disagree and submit that *at most* this provides motivation to attempt to clone or characterize such variants. Tartaglia et al. merely speculates regarding spliced forms, where it states at page 1268:

> Another possibility is that, in some tissues, alternatively spliced forms of mouse OB-R exist with longer intracellular domains. Support for this hypothesis comes from our identification of a human OB-R homolog with a long intracellular domain. Furthermore, the Class I cytokine receptors to which OB-R is most closely related are the gp130 signal-transducing component of the IL-6 receptor (Taga et al., 1989), the

G-CSF receptor (Fukunaga et al., 1990a; Larsen et al., 1990), and the LIF receptor (Gearing et al., 1991), all of which have long intracellular signaling domains.

There is no teaching of the actual existence of any such possible variant OB-R forms, nor is there any reasonable characterization of such forms, if they even do exist.

With respect to Snodgrass et al, the Examiner remarks that Snodgrass et al disclose a novel hemopoietin receptor having a WSX motif and having sequence homology to other hemopoietin receptors such as Il-6R and that the receptor of Snodgrass is now known as one form of the OB/leptin receptor. The Examiner asserts that although Snodgrass et al does not refer their receptor as the ob/leptin receptor, and does not expressly teach alternative or variant forms, "the teaching at col 15 in conjunction with the teachings at col 4 lines 19-39 provide clear motivation for the skilled artisan to use the DNA to probe a genomic library to obtain variant forms of the receptor (See Ex parte Anderson, 30 USPQ d. 1867) - thus, rendering obvious the instant claims that recite a DNA sequence that is different from that disclosed in the prior art". Applicants respectfully disagree and submit that Snodgrass et al neither teaches or discloses any such possible receptor variants as claimed by Applicants. In addition, reference in Snodgrass et al. to the "possible existence of other splice variants", as noted by the Examiner, does not render the variants of the instant invention obvious.

In view of the foregoing remarks, Applicants request that the Examiner's rejections under 35 U.S.C. 102 or 103 be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,

KLAUBER & JACKSON

Original signed by CED 7/7/98

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